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January 11, 2005

Mail Stop Appeal Brief - Patent Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Re:

U.S. Application No. 09/394,745

Filed: September 15, 1999

Title: Nucleic Acid Molecules and Other Molecules Associated

with Plants

Applicants: Dane K. FISHER *et al.*Atty. Docket: 16517.280/38-21(15454)B

Sir:

The following documents are forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

- 1. an Appellants' Reply Brief; and
- 2. a return postcard.

Please stamp the attached postcard with the filing date of these documents and return it to our courier.

In the event that extensions of time beyond those petitioned for herewith are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned. Applicants do not believe any fees are due in conjunction with this filing. However, if any fees are required in the present application, including any fees for extensions of time, then the Commissioner is hereby authorized to charge such fees to Arnold & Porter LLP Deposit Account No. 50-2387 referencing matter number 16517.280. A duplicate copy of this letter is enclosed.

Respectfully submitted,

David R. Marsh (Reg. Atty. No. 41,408)

Holly Logue Prutz (Reg. Attorney No. 47,755)

Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARDOF PATENT APPEALS AND INTERFERENCES

In re application of:

Confirmation No.: 4816

Art Unit:

1637

Appln. No.: 09/394,745

Dane K. FISHER et al.

Examiner:

Young J. KIM

Filed:

September 15, 1999

Atty. Docket:

16517.280/38-21(15454)B

For:

Nucleic Acid Molecules and Other Molecules Associated with Plants

APPELLANTS' REPLY BRIEF

Mail Stop Appeal Brief – Patent Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450

Sir:

This is a reply to arguments raised in the Examiner's Answer mailed November 12, 2004 ("Second Examiner's Answer").

In the event that extensions of time beyond those petitioned for herewith are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned. Appellants do not believe any additional fees are due in conjunction with this filing. However, if any fees under 37 C.F.R. §§ 1.16 or 1.17 are required in the present application, including any fees for extensions of time, authorization to charge such fees is given in the accompanying transmittal letter.

1. Introduction

The Second Examiner's Answer is in response to Appellants' second Appeal Brief filed June 30, 2003 ("Second Appeal Brief"), which addresses what Appellants regard as their invention and the improper restriction requirement. See, e.g., Second Appeal Brief at 3-5. The Second Examiner's Answer states that:

- the restriction requirement has been withdrawn, thus "rendering Appellants' arguments made [in the Second Appeal Brief] moot." Second Examiner's Answer at 2-3.
- "the resulting combination of the nucleic acids, includes a novel SEQ ID Number SEQ ID NO: 5893... resulting in a novel combination of nucleic acids." Second Examiner's Answer at 3.
- the issues remaining in Application Ser. No. 09/394,745 (the "Application") are the same as those raised in Examiner's Answer mailed May 23, 2003 ("First Examiner's Answer"). See Second Examiner's Answer at 3.

Appellants submit this Reply Brief to address the issues raised by these statements. Further, Appellants submit that the outstanding rejections under 35 U.S.C. §§ 101 and 112, first paragraph, are improper.

2. The Examiner is Incorrect in Asserting that the Second Appeal Brief is Moot

Withdrawal of the restriction requirement does not render the Second Appeal Brief moot because the inventions of the examined, restricted claims are significantly different from the inventions of the non-examined, non-restricted claims. As noted in the Second Appeal Brief, Appellants' non-restricted invention is not drawn to "individual"

¹ While Appellants believe they should prevail on the merits in the present appeal, should the Board of Patent Appeals and Interferences (the "Board") remand the Application, Appellants request that the Board specifically remand the case with an instruction to examine the full scope of the claims, without restriction.

nucleic acid molecules that purportedly constitute independent and distinct inventions."² Instead, Appellants' non-restricted invention is directed to "a microarray constituted by a combination of nucleic acid molecules that can be modified by its user to select for specific nucleic acid molecules of interest in a given sample."³ As more specifically stated in Appellants' Second Appeal Brief:

Applicants' invention is a microarray in which no single variation is characteristic of the claimed microarray, rather it is the ability to modify, substitute and select different collections or combinations of recited nucleic acid molecules, including the ability to choose precisely which molecules to include or exclude from those listed in the recited group, that creates the essence of Applicants' invention. Applicants' invention is not a fixed microarray, but rather the invention provides the ability to vary the contents of a microarray within the parameters set forth in the claim.⁴

The Second Examiner's Answer fails to consider that the claimed invention is "a microarray constituted by a combination of nucleic acid molecules that can be modified by its user to select for specific nucleic acid molecules of interest in a given sample." Instead, the focus of the Second Examiner's Answer is "individual nucleic acid molecules that purportedly constitute independent and distinct inventions." By focusing on the utility and written description requirements of nucleic acid molecules rather than the claimed microarray, the Examiner has failed to apply an appropriate analysis under 35 U.S.C. §§ 101 and 112.

² Second Appeal Brief at 8.

³ *Id*.

⁴ Id. at 9-10.

⁵ Second Appeal Brief at 8.

3. The Office Has Applied an Incorrect Utility Analysis to the Claimed Invention and Mischaracterizes the Non-Restricted Claims

The Second Examiner's Answer asserts that "the resulting combination of the nucleic acids, includes a novel SEQ ID Number - SEQ ID NO: 5893... resulting in a novel combination of nucleic acids." Second Examiner's Answer at 3. It is incorrect that the claims require SEQ ID NO: 5893 as this ignores the language of non-restricted claims 8-10 (attached hereto as Appendix A). These claims are not, and have never been, limited to a microarray comprising a particular combination of nucleic acid sequences that must always include SEQ ID NO: 5893. Second Examiner's Answer at 3. See also Appendix A. While it is true that, with the withdrawal of the restriction requirement, the claimed microarray includes various combinations of nucleic acid molecules, it is not correct to assume or require that any combination must always include SEQ ID NO: 5893. This mischaracterization of the claimed invention in the Second Examiner's Answer results in an incorrect analysis under 35 U.S.C. §§ 101 and 112 that focuses on an individual nucleic acid molecule rather than the claimed microarrays. Moreover, the analysis is improper because it ignores the utility of a claimed microarray which is fundamentally different from the utility of one of its elements, i.e. a single nucleic acid molecule.6

⁶ See, e.g., Request for Reconsideration of Applicants' Petition under 37 C.F.R. § 1.181, filed January 12, 2004 ("Second Request"), at 4-8).

- 4. The Office Continues to Misread the Invention and Misstates the Utility Analysis of the Claimed Invention
 - a. The Office Has Acknowledged that Microarrays Comprising a Plurality of *Unidentified* Oligonucleotides Meet the Utility Standard of 35 U.S.C. § 101

The Second Examiner's Answer acknowledges that the microarray described and claimed in U.S. Patent No. 5,445,934, which "claims an array of oligonucleotides without specific sequences," meets the utility standard. Second Examiner's Answer at 9. Specifically, the Second Examiner's Answer states:

Appellants confuse the patentability of a general microarray versus the microarray of the instant application. The '934 patent is drawn to a microarray comprising a plurality of oligonucleotides (not specific sequences) and patented by its utility for being able to analyze a plurality of nucleic acid samples simultaneously (including being able to analyze binding affinities). *This is a practical and immediately apparent utility*. However, the utility of the present microarray is directly dependent upon the nucleic acid molecules which the microarray comprises.

Id. (emphasis added). What the Office has neglected to recognize is that the claimed microarrays have the exact features relied upon by the Office to support the utility of the microarray claimed in the '934 patent. For example, the claimed microarray is useful for being able to analyze a plurality of nucleic acid samples simultaneously. Moreover, the claimed microarray is also useful for screening "protein molecules or fragments thereof or nucleic acid molecules in order to screen for either protein molecules or fragments thereof or nucleic acid molecules that specifically bind the target polypeptides."

Despite the admission by the Office that an *uncharacterized* microarray has utility, the Office still improperly contends that "Appellants fail to provide a substantial

⁷ Specification at page 60, lines 21-23. See also Appeal Brief filed March 13, 2003 ("First Appeal Brief"), at 8-11 (discussing the utility of the claimed microarray to assess relative binding efficiencies of bound molecules).

utility of the claimed nucleic acid molecules on the microarray, thereby failing to give substantial utility to the claimed microarray." Examiner's Answer at 14. Appellants have repeatedly stated that this position ignores the claimed invention and is an improper utility analysis of the non-restricted claims. See, e.g., Second Request at 3-8. In the Second Request, Appellants presented the analogy of the claimed microarray to a piano. Id. at 4-8. The Examiner's treatment of the claimed microarray very much mirrors the examination of a single key of a piano. The utility of that single key is very different than the utility of the piano as a whole. Id. at 6-7. Here, the Examiner has merely examined a single key and determined that since that key alone allegedly does not have utility, then neither does the piano. This is not the law. In much the same way as the utility of a single key in a piano cannot be equivalent to the utility of the piano itself, the utility of a nucleic acid molecule cannot be equated to the utility of a microarray.

b. The Office Focuses Its Analysis on the Underlying Nucleic Acid Molecules and Ignores that the Claimed Invention is a Microarray

The utility analysis in the Second Examiner's Answer improperly focuses on the utility of an optional element of a claimed microarray, not on the microarray itself. For example, the Examiner argues that "[n]o traits are attributed to the combination of the recited SEQ ID Numbers. No complete gene is disclosed nor DNA maps/chromosomal location is identified. No polymorphisms are identified." Second Examiner's Answer at 5. The Examiner also states that "[t]he nucleic acid molecules which make up the claimed microarray are starting materials for further research and not research tools," *Id.*, and "the claimed nucleic acids are admitted as having no known utility." *Id.* at 7. This

⁸ The Second Examiner's Answer concludes that Appellants' statement that it "is irrelevant whether the corresponding mRNA or polypeptide have utility because Applicants are not relying on utility of the mRNA or polypeptide to establish utility of the claimed microarrays" is an admission that the claimed microarray lacks <u>legal</u> utility. Whatever else this statement might be, it is not such an admission.

analysis incorrectly focuses on the utility of the nucleic acid molecules, <u>not</u> the acknowledged utility of the claimed microarray. Moreover, this argument is objectively incorrect in that microarrays containing uncharacterized DNA are recognized by those of skill in the art as having practical utility in genetic research, drug discovery, comparative analysis, etc.⁹

Appellants note the Second Examiner's Answer is virtually *identical* to the Examiner's Answer mailed May 23, 2003 ("First Examiner's Answer"), where the Office considered the invention in light of the restriction requirement. Such an approach fails to consider that the restricted and non-restricted claims claim different inventions. During the prosecution of this application Appellants have repeatedly stated that the invention is not a single nucleic acid molecule, or even a combination of nucleic acid molecules that always include SEQ ID NO: 5893. *See, e.g.,* Petition under §1.144, filed January 10, 2003 ("First Petition"), at 7-10; First Appeal Brief at 7-11; Request for Reconsideration of Applicant's Petition, filed April 14, 2003 ("First Request"), at 3-6; Second Appeal

From: http://www.cs.wustl.edu/~jbuhler/research/array/ (emphasis added).

⁹ Those of skill in the art widely recognize the utility of microarrays in genetic research, drug discovery, comparative analysis, etc., even where the nucleic acid molecules included on the microarray are "uncharacterized". For example, the following describes the use of microarrays to study human genes:

Because the human genome has not been completely sequenced, we cannot yet produce a comprehensive array for all its genes. Moreover, the number of human genes has been estimated at somewhere between 10,000 and 100,000, so several arrays will probably be required to hold them all. Despite these limitations, several strategies can be used today to make arrays for studying human genes. We do know the location and sequence of quite a few human genes now, so the same method used to array yeast genes will produce at least a partial human genome array. There are two other ways to produce arrayable DNA even for unknown genes: amplify clone inserts from human cDNA libraries, or synthesize oligonucleotides directly from known expressed sequence information such as EST's [sic]. While neither of these methods will produce DNA's [sic] for every human gene, both can yield enough different expressed sequences to make substantial arrays. Both types of DNA have been used before in array-like applications: cDNA libraries were used for comparative hybridization before the advent of fluorescent microarrays, while oligonucleotide arrays are available commercially today from Affymetrix Corporation for rapid resequencing of a few genes important to AIDS and some cancers.

Brief at 6-7.¹⁰ Moreover, Appellants have stated that it is not the presence of any single nucleic acid sequence included on the claimed microarray itself that lends support to the utility of the claimed invention.¹¹ See, e.g., Second Appeal Brief at 9-10. It is the microarray itself and the ability to elect various combinations of the identified SEQ ID Numbers to include in (or exclude from) the claimed microarray that provide the utility of the claimed invention.

5. The Claimed Invention is Enabled

Because the Examiner has acknowledged utility of a non-restricted, claimed microarray, the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement cannot stand. *See* Second Examiner's Answer at 9, First Examiner's Answer at 8.

6. The Office Fails to Consider Appropriate Precedent in the Written Description Analysis of the Claimed Invention

The Examiner's analysis of the claimed invention has missed this point and contradicts its treatment of other microarray inventions. The Examiner has rejected claims 8-11 based on 35 U.S.C. § 112, first paragraph, as lacking adequate written description. The Second Examiner's Answer argues that

[t]he use of the term "comprising" is interpreted to encompass nucleic acid molecules with a complete open reading frame, which have not been disclosed or identified. The specification described only the recited SEQ ID Numbers and no

¹⁰ An interview with the group director resulted in a decision to withdraw the requirement. *See* Interview Summary dated August 19, 2004.

The Second Examiner's Answer asserts that the Appellants have not provided the necessary nexus between the claimed arrays and the "real world" use. Second Examiner's Answer at 4. Appellants disagree for the reasons set forth in the First Appeal Brief at 4-13. However, Appellants note that the removal of the restriction requirement by the Examiner occurred after the filing of the First Appeal Brief, the Second Appeal Brief, the First Examiner's Answer, the First Petition, the First Request, Applicants' Petition under 37 C.F.R. § 1.181, filed July 9, 2003 ("Second Petition"), and the Second Request, preventing Appellants from providing additional evidence. If the Board determines that the present record is insufficient to establish utility, Appellants request that the Board remand the case to the Examiner to allow the Appellants an opportunity to provide additional evidence.

longer sequences containing them. One can only envision the particular polynucleotide with the disclosed sequence and cannot envision polynucleotide [sic] with a larger sequence in which the claimed polynucleotide(s) with the recited SEQ ID Numbers are embedded.

Second Examiner's Answer at 6. The Second Examiner's Answer also contends that

[t]he specification fails to provide structural and functional characteristic [sic] for nucleic acid molecules comprising full-open reading frames that would distinguish them from other members of the genus, which simply comprise the recited SEQ ID Numbers as the sole distinguishing feature.

Id. at 18.

At the outset, Appellants' claims are directed to a microarray comprising nucleic acid molecules that are comprised of different sequences and are not directed to an individual sequence. Appellants have provided an adequate description of the claimed microarray that demonstrates to one skilled in the art that Appellants had possession of the claimed invention.

a. The Specification Reflects Appellants' Possession of the Claimed Invention

The purpose of the written description requirement is to ensure that the inventors had possession of the claimed subject matter, *i.e.*, to ensure that the inventors actually invented what is claimed. *Gentry Gallery Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479, 45 U.S.P.Q.2d 1498, 1503 (Fed. Cir. 1998); *Lockwood v. American Airlines*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966(Fed. Cir. 1997); *In re Alton*, 76 F.3d 1168, 1172, 37 U.S.P.Q.2d 1578, 1581 (Fed. Cir. 1996). If a person of ordinary skill in the art would, after reading the specification, understand that the inventors had possession of the claimed invention, even if not every nuance, then the written description has been met. *In re Alton*, 76 F.3d at 1175, 37 U.S.P.Q.2d at 1584. A person of ordinary skill in the art, *e.g.*, a molecular biologist, would, after reading the present specification, understand that Appellants had possession of the microarray and therefore, the claimed invention.

Moreover, Appellants have provided the nucleotide sequence recited by the claims ¹² and have thus established possession of the claimed invention. The fact that the microarrays are intended to include molecules that include the recited sequences joined with additional sequences does not mean that Appellants were any less in possession of the nucleic acid molecules embedded on the claimed microarray. It is well-established that use of the transitional term "comprising" leaves the claims "open for the inclusion of unspecified ingredients even in major amounts." *Ex parte Davis*, 80 U.S.P.Q. 448, 450 (B.P.A.I. 1948). *Accord PPG Indus. v. Guardian Indus.*, 156 F.3d 1351, 1354, 48 U.S.P.Q.2d 1351, 1353-54 (Fed. Cir. 1998); *Moleculon Research Corp. v. CBS*, 793 F.2d 1261, 1271, 229 U.S.P.Q. 805, 812 (Fed. Cir. 1986).

b. Appellants Have Described the Claimed Invention

The Second Examiner's Answer asserts that "[t]he specification fails to provide structural and functional characteristic [sic] for nucleic acid molecules comprising full-open reading frames that would distinguish them from other members of the genus, which simply comprise the recited SEQ ID Numbers as the sole distinguishing feature." Second Examiner's Answer at 18. The Second Examiner's Answer appears to assert that each nucleic acid molecule within the genus must be "described by complete structure." Second Examiner's Answer at 16. These assertions are totally unfounded. An adequate written description of a genus of nucleic acids may be achieved by a "recitation of structural features common to the members of the genus." Regents of the University of

¹² SEQ ID NOs: 5776, 5781, 5782, 5783, 5785, 5787, 5800, 5804, 5815, 5818, 5821, 5823, 5828, 5830, 5832, 5836, 5838, 5840, 5845, 5849, 5850, 5851, 5856, 5859, 5863, 5868, 5871, 5874, 5875, 5877, 5893, 5896, 5901, 5908, 5909, 5920, 5922, 5926, 5928, 5929, 5931, 5936, 5937, 5939, 5941, 5944, 5945, 5950, 5955, 5960, 5961, 5963, 5964, 5968, 5973, 5974, 5991, 5994, 5999, 6000, 6001, 6005, 6006, 6007, 6011, 6017, 6018, 6022, 6023, 6026, 6030, 6033, 6042, 6046, 6059, 6063, 6065, 6066, 6089, 6091, 6098, 6106, 6107, 6110, 6117, 6121, 6124, 6131, 6137, 6141, 6144, 6145, 6147, 6154, 6167, 6168, 6170, 6173, 6178, and 6181.

California v. Eli Lilly and Co., 119 F.3d 1559, 1568-69, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). The structural feature relied upon to describe the claimed genus must be capable of distinguishing members of the claimed genus from non-members. ¹³ Id.

The nucleic acid molecules of the claimed microarray are genera of nucleic acid molecules having common structural features represented by their respective SEQ ID Numbers. Every nucleic acid molecule in each genus shares these common structural features, and this distinguishes the members of that genus from non-members. For example, if a nucleic acid molecule such as an mRNA contains SEQ ID NO: 5776, then it is a member of that genus. ¹⁴ If a nucleic acid molecule does not contain SEQ ID NO: 5776, then it is not a member of that genus. The presence of other nucleotides at either end of the recited sequence will not interfere with the recognition of a nucleic acid molecule present in the claimed microarray as such – it either contains the nucleotides of SEQ ID NO: 5776 or it does not.

¹³ The Second Examiner's Answer confuses the issue by asserting that "the specification fails to provide structural and functional characteristics of [full length mRNAs, cDNAs and genomic sequences comprising SEQ ID NO: 1] for nucleic acid molecules comprising full-open reading frames..." Second Examiner's Answer at 18. This assertion has no basis in law. The Federal Circuit has elucidated a test for written description wherein a genus of nucleic acids may be described by a structural feature that distinguishes members of the claimed genus from non-members of the claimed genus. Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568-69, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997).

¹⁴ This same argument applies with equal force to each genus of nucleic acid molecules in the recited group of the claimed microarray. For example, if a nucleic acid molecule such as an mRNA contains SEQ ID NO: 5823, then it is a member of the genus of nucleic acid molecules comprising a sequence of SEQ ID NO: 5823 and, provided it fulfills the other elements of the claimed invention, it would be considered one of the nucleic acid molecules that may be selected to be included on the claimed microarray.

CONCLUSION

In view of the arguments above, Appellants specifically request that the Board of Patent Appeals and Interferences reverse the Rejections.

Respectfully submitted,

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Appendix A: Pending Claims

8. A microarray comprising a substrate with a surface comprising 10³ nucleic acid molecules or more where at least 10% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from the group consisting of SEQ ID NO: 5776, SEQ ID NO: 5781, SEQ ID NO: 5782, SEQ ID NO: 5783, SEQ ID NO: 5785, SEQ ID NO: 5787, SEQ ID NO: 5800, SEQ ID NO: 5804, SEQ ID NO: 5815, SEQ ID NO: 5818, SEQ ID NO: 5821, SEQ ID NO: 5823, SEQ ID NO: 5828, SEQ ID NO: 5830, SEQ ID NO: 5832, SEQ ID NO: 5836, SEQ ID NO: 5838, SEQ ID NO: 5840, SEQ ID NO: 5845, SEQ ID NO: 5849, SEQ ID NO: 5850, SEQ ID NO: 5851, SEQ ID NO: 5856, SEQ ID NO: 5859, SEQ ID NO: 5863, SEQ ID NO: 5868, SEQ ID NO: 5871, SEQ ID NO: 5874, SEQ ID NO: 5875, SEQ ID NO: 5877, SEQ ID NO: 5893, SEQ ID NO: 5896, SEQ ID NO: 5901, SEQ ID NO: 5908, SEQ ID NO: 5909, SEQ ID NO: 5920, SEQ ID NO: 5922, SEQ ID NO: 5926, SEQ ID NO: 5928, SEQ ID NO: 5929, SEQ ID NO: 5931, SEQ ID NO: 5936, SEQ ID NO: 5937, SEQ ID NO: 5939, SEQ ID NO: 5941, SEQ ID NO: 5944, SEQ ID NO: 5945, SEQ ID NO: 5950, SEQ ID NO: 5955, SEQ ID NO: 5960, SEQ ID NO: 5961, SEQ ID NO: 5963, SEQ ID NO: 5964, SEQ ID NO: 5968, SEQ ID NO: 5973, SEQ ID NO: 5974, SEQ ID NO: 5991, SEQ ID NO: 5994, SEQ ID NO: 5999, SEQ ID NO: 6000, SEQ ID NO: 6001, SEQ ID NO: 6005, SEQ ID NO: 6006, SEQ ID NO: 6007, SEQ ID NO: 6011, SEQ ID NO: 6017, SEQ ID NO: 6018, SEQ ID NO: 6022, SEQ ID NO: 6023, SEQ ID NO: 6026, SEQ ID NO: 6030, SEQ ID NO: 6033, SEQ ID NO: 6042, SEQ ID NO: 6046, SEQ ID NO: 6059, SEQ ID NO: 6063, SEQ ID NO: 6065, SEQ ID NO: 6066, SEQ ID NO: 6089, SEQ ID NO: 6091, SEQ ID NO: 6098, SEQ ID NO: 6106, SEQ ID NO: 6107, SEQ ID NO: 6110, SEQ ID NO: 6117, SEQ ID NO: 6121, SEQ ID NO: 6124, SEQ ID NO: 6131, SEQ ID NO: 6137, SEQ ID NO: 6141, SEQ ID NO: 6144, SEQ ID NO: 6145, SEQ ID NO: 6147, SEQ ID NO: 6154, SEQ ID NO: 6167, SEQ ID NO: 6168, SEQ ID NO: 6170, SEQ ID NO: 6173, SEQ ID NO: 6178, and SEQ ID NO: 6181.

- 9. A microarray according to claim 8 where at least 75% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from said group.
- 10. A microarray according to claim 8 where at least 95% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from said group.